The role of the methylation of the progesterone receptor isoforms A and B promoters in the regulation of bovine corpus luteum function

The corpus luteum (CL) is an important endocrine gland and is found in the ovaries of sexually mature females during the estrous cycle and at the early stages of pregnancy. It is formed after the release of the oocyte at the site of the ruptured follicle. Lack of potential pregnancy leads to degradation of CL structures at the end of the cycle and is known as luteolysis. In contrast, in pregnancy, CL continues its functioning as the Corpus Luteum graviditatis. The corpus luteum is responsible for the production of progesterone (P4), one of the main steroidal sex hormones. It is responsible for the creation of suitable conditions for embryo implementation and the proper course of pregnancy. Progesterone action in target tissues is mainly carried out by the nuclear receptor (PGR) belonging to the family of transcription factors. This receptor occurs in the form of two main isoforms A (PGRA) and B (PGRB). The proper functioning of PGR is an important factor regulating the CL function. Any disturbances in their functioning often lead to pathological conditions in pregnancy and miscarriages in both farm animals and humans. Receptor function is regulated at various molecular levels. Changes in the level of expression of the PGR gene or in the level of coregulators attaching to the receptor during its activation and also the regulation of its activity by P4 itself are some of the most important. Another level of regulation may be changing the methylation level of the promoters of the receptor isoforms. This process involves the addition of a methyl group by a methyltransferase (DNMT1) to the cytosine nucleotide, which changes the availability of the polymerase to the promoter of a given gene. Thus, it indirectly influences the initiation of the process of its expression. An important role in DNA demethylation is played by TET proteins (ten-eleven translocation proteins) belonging to the dioxygenase family. The three TET proteins (TET1-3) oxidize 5-mc to 5-hydroxymethylcytosine causing abolition of methylation.

Therefore, the main goal of this project is to investigate the participation of the methylation of the progesterone receptor PGRA and PGRB promoters in the regulation of the corpus luteum of the cow. In individual tasks, we will determine whether luteotropic and luteolytic factors regulate methylation through changes in DNMT1 expression and DNMT1 methyltransferase activity; whether there are processes of active demethylation involving cytosine hydroxymethylation during the estrous cycle in the reproductive system; whether P4 can regulate methylation at the global level in the CL. This project aims to broaden the existing knowledge on the effects of methylation in the reproductive system. Understanding this type of regulation within the promoters of the progesterone receptor A and B isoforms may be important in understanding pregnancy disorders in cows and possibly other species.